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(21) International Application Number: PCT/US91/03185 (22) International Filing Date: 13 May 1991 (13.05.91) (30) Priority data: 522,145 11 May 1990 (11.05.90) US (60) Parent Application or Grant (63) Related by Continuation US 522,145 (CIP) Filed on 11 May 1990 (11.05.90) (71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL COMPANY, LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).		(72) Inventors; and (75) Inventors/Applicants (for US only) : KUBES, Paul [US/ US]; 5720 South Lakeshore Drive, Apartment 1406, Shreveport, LA 71119 (US). HUNTER, James [US/US]; 2057 Holly Oak Drive, Shreveport, LA 71119 (US). GRANGER, D., Neil [US/US]; 2108 Chase Wells, Shreveport, LA 71119 (US). (74) Agents: OBLON, Norman, F. et al.; Oblon, Spivak, McClelland, Maier & Neustadt, Fourth Floor, 1755 South Jefferson Davis Highway, Arlington, VA 22202 (US). (81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (Eu- ropean patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European pa- tent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>
(54) Title: METHODS FOR TREATING AND PREVENTING INFLAMMATION OF MUCOSA AND BLOOD VESSELS USING FK 506 AND RELATED COMPOUNDS (57) Abstract Macrolide compounds are useful for the prevention and treatment of inflammation of mucosa and blood vessels and dis- eases such as LTB ₄ -mediated diseases, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel disease, inflammatory bowel disease, necrotizing enterocolitis, and intestinal lesions associated with thermal burns.		

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DescriptionMethods for Treating and Preventing Inflammation
of Mucosa and Blood Vessels Using FK 506
and Related Compounds5 Technical Field

 The present invention relates to the use of
macrolide compounds, such as FK 506, for treating or
preventing inflammation of mucosa and blood vessels, such
as gastric ulcers, vascular damage caused by ischemic
10 diseases and thrombosis, ischemic bowel disease,
inflammatory bowel disease and necrotizing enterocolitis.

Background Art

 Inflammation of mucosa and blood vessels often
results from the reperfusion of ischemic tissue such as
15 intestines. Diseases which involve inflammation of
mucosa and vascular tissue include ischemic bowel
disease, inflammatory bowel disease, necrotizing
enterocolitis, gastric ulcers and vascular damage caused
by ischemic diseases and thrombosis. Leukocyte
20 infiltration is a characteristic feature of tissue injury
(Adams et al, Gastroenterology, Vol. 97, p. 433 (1989)),
and it is often assumed that neutrophils play a more
important role in mediating the injury associated with
reperfusion while lymphocytes primarily contribute to the
25 rejection phase (Craddock et al, Transplantation, Vol.
35, p. 284 (1983)). In addition, intestinal ischemia is
a complication in patients suffering from thermal burns
(Desai et al, Surgery Gynecology and Obstetrics, vol.
172, pp. 257-261 (April, 1991)).

30 Recent evidence suggests that cyclosporin A
attenuates reperfusion injury. However, the effect of
cyclosporin A for the treatment or prevention of
inflammation of mucosa and blood vessels is not

sufficiently effective. Accordingly, there remains a need for a method of treating or preventing the inflammation of mucosa and blood vessels and the above-mentioned diseases.

5 Disclosure of the Invention

Accordingly, one object of the present invention is to provide a method for preventing or treating inflammation of mucosa or blood vessels.

10 A further object is to provide a method for preventing or treating ischemic bowel disease.

It is another object of the present invention to provide a method for preventing or treating inflammatory bowel disease.

15 It is another object of the present invention to provide a method for preventing or treating necrotizing enterocolitis.

It is another object of the present invention to provide a method for preventing or treating gastric ulcers.

20 It is another object of the present invention to provide a method for preventing or treating vascular damage resulting from ischemic diseases and thrombosis.

25 It is another object of the present invention to provide a method for minimizing intestinal lesions associated with thermal burns.

It is another object of the present invention to provide a method for preventing or treating LTB₄-mediated diseases.

These and other objects, which will become clear in the course of the following detailed description, have been achieved by the present method which involves the administration of an effective amount of a macrolide
5 compound.

Brief Description of the Drawings

A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same become better understood by
10 reference to the following detailed description when considered in connection with the accompanying drawings, wherein:

Figure 1 illustrates the increase in mucosal myeloperoxidase activity during ischemia and following
15 reperfusion in untreated, cyclosporin A-pretreated and FK 506-pretreated animals indicates (* <0.05 relative to the corresponding time period in the untreated group); and

Figure 2 illustrates the mucosal leukotriene B₄ concentration during control, ischemia and reperfusion in
20 the untreated, cyclosporin A- and FK 506-pretreated animals (* indicates p<0.05 relative to the corresponding time period in the untreated group).

Best Mode for Carrying Out the Invention

25 It has now been discovered that by administration of the macrolide compounds of the present invention to a mammal, inflammation of mucosa and blood vessels may be treated or prevented. The macrolide compounds of the present invention are therefore useful to treat diseases
30 which result in the inflammation of mucosa and blood vessels, such as ischemic bowel disease, inflammatory

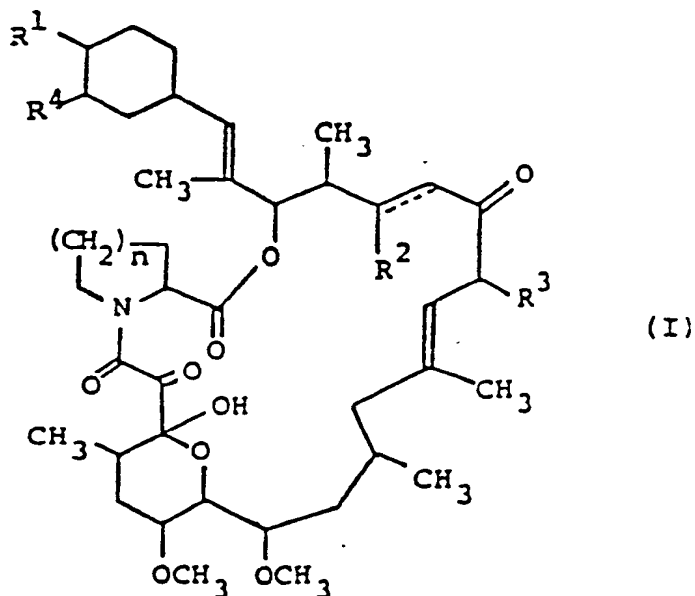
bowel diseases (e.g., Crohn's disease and ulcerative colitis), necrotizing enterocolitis, gastric ulcers and vascular damage caused by ischemia and thrombosis.

5 The macrolide compounds utilized in the present invention, in particular the macrolide FK 506, are known immunosuppressive compounds which prevent acute and chronic liver allograft rejection in humans (Starzl et al, Lancet, 1989, 2:1000-1004). Several compounds
10 belonging to this class of immunosuppressive macrolides are obtained from cultures of species belonging to the genus Streptomyces. Compounds within this class are described in U.S. Patents 4,894,366 and 4,929,611 and U.S. Patent Application Serial No. 07/386,233, filed July 28, 1989.

15 The high efficacy of the present compounds to reduce the inflammation of mucosa and blood vessels and to treat the present diseases is surprising, since other compounds which exhibit immunosuppressive properties are not as effective. For example, cyclosporin A which exhibits
20 immunosuppressive activity is much less effective in the treatment and/or prevention of inflammation of mucosa and blood vessels than the present compounds.

 The present macrolide compounds are believed to mediate the inflammation of mucosa and blood vessels by
25 reducing the neutrophil infiltration into mucosa.

The macrolide compounds useful in the present invention are compounds having structure I shown below.



In structure I, R¹ is hydroxy or protected hydroxy, R² is hydrogen, hydroxy or protected hydroxy, R³ is methyl, ethyl, propyl or allyl, R⁴ is hydroxy, methoxy or oxo (=O), n is an integer of 1 or 2 and the symbol of a line and a dotted line is a single bond or a double bond, provided that R² is not protected hydroxy when R⁴ is hydroxy or oxo, and salts thereof.

Such macrolide compounds may be prepared by both fermentation processes and synthetic organic processes as disclosed in U.S. Patent Nos. 4,894,366, and 4,929,611, and U.S. Patent Application Serial No. 07/386,233, filed July 28, 1989. These U.S. patent applications are incorporated herein by reference for a more complete description of the compounds having structure I, their preparation and properties.

The term "lower" used in the specification is intended to mean 1 to 6 carbon atoms, unless otherwise

indicated.

Suitable hydroxy-protective groups in the "protected hydroxy" may include: 1-(lower alkylthio) (lower) alkyl such as lower alkylthiomethyl (e.g. methylthiomethyl, 5 ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), and the like, in which the preferred one is C₁-C₄ alkylthiomethyl and the most preferred one is methylthiomethyl; trisubstituted silyl such as tri(lower) 10 alkylsilyl (e.g. trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyl-dimethylsilyl, tri-tert-butylsilyl, etc.), lower alkyl-diarylsilyl (e.g. methyl-diphenylsilyl, ethyl-diphenylsilyl, propyl-diphenylsilyl, tert-butyl-diphenylsilyl, etc.), and the like, in which 15 the preferred one is tri(C₁-C₄)alkylsilyl and C₁-C₄ alkyl-diphenylsilyl, and the most preferred one is tert-butyl-dimethylsilyl and tert-butyl-diphenylsilyl; acyl such as aliphatic acyl, aromatic acyl and aliphatic acyl substituted with aromatic groups, which are derived from 20 carboxylic, sulfonic and carbamic acids; and the like.

The aliphatic acyl may include lower alkanoyl which may have one or more suitable substituent(s) such as carboxy (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, 25 carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl, etc.), cyclo(lower)alkyloxy-(lower)alkanoyl which may have one or more suitable substituent(s) such as lower alkyl (e.g. cyclopropyloxyacetyl, cyclobutyloxypropionyl, 30 cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxypropionyl, menthyloxybutyryl, menthyloxyhexanoyl, etc.), camphorsulfonyl, lower alkylcarbamoyl having one or more

suitable substituent(s) such as carboxy and a protected carboxy, for example, carboxy(lower)alkylcarbamoyle (e.g. carboxymethylcarbamoyle, carboxyethylcarbamoyle, carboxypropylcarbamoyle, carboxybutylcarbamoyle, carboxypentylcarbamoyle, carboxyhexylcarbamoyle, etc.,
5 protected carboxy(lower)alkylcarbamoyle such as tri(lower)alkylsilyl(lower)alkoxycarbonyl(lower)alkylcarbamoyle (e.g. trimethylsilylmethoxycarbonylethylcarbamoyle, trimethylsilylethoxycarbonylpropylcarbamoyle,
10 triethylsilylethoxycarbonylpropylcarbamoyle, tertbutyldimethylsilylethoxycarbonylpropylcarbamoyle, trimethylsilylpropoxycarbonylbutylcarbamoyle, etc.), and the like.

The aromatic acyl may include aroyl which may have
15 one or more suitable substituent(s) such as nitro (e.g. benzoyl, toluoyl, xyloyle, naphthoyle, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyle, etc.), arenesulfonyl which may have one or more suitable substituent(s) such as halogen (e.g. benzenesulfonyl, toluenesulfonyl,
20 xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.), and the like.

The aliphatic acyl substituted with aromatic group
25 may include ar(lower)alkanoyl which may have one or more suitable substituent(s) such as lower alkoxy and trihalo(lower)alkyl (e.g. phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl,
30 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.), and the like.

The more preferred acyl group thus defined is C₁-C₄

alkanoyl which may have carboxy, cyclo(C₃-C₆)alkyloxy(C₁-C₄)alkanoyl having two (C₁-C₄) alkyl groups on the cycloalkyl moiety, camphorsulfonyl, carboxy (C₁-C₄)-alkylcarbamoyl, tri(C₁-C₄)alkylsilyl(C₁-C₄)alkoxycarbonyl-
5 (C₁-C₄)alkylcarbamoyl, benzoyl which may have one or two nitro groups, benzenesulfonyl having halogens, phenyl(C₁-C₄)alkanoyl having C₁-C₄ alkoxy and trihalo (C₁-C₄) alkyl, and the most preferred are acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl,
10 dinitrobenzoyl, iodobenzenesulfonyl and 2-trifluoromethyl-2-methoxy-2-phenylacetyl.

Particularly preferred macrolide compounds include:

(1) the macrolide compound in which R¹ and R² are each hydroxy, R³ is allyl, R⁴ is methoxy, n = 2, and the
15 symbol of a line and a dotted line is a single bond.

This compound is known as FR-900506 or FK 506;

(2) the compound in which R¹ and R² are each hydroxy, R³ is ethyl, R⁴ is methyl, n = 2, and the symbol of a line and a dotted line is a single bond. This
20 compound is also known as FR-900520 or WS 7238A;

(3) the compound in which R¹ and R² are each hydroxy, R³ is methyl, R⁴ is methyl, n = 2, and the symbol of a line and a dotted line is a single bond. This compound is known as FR-900523 or WS 7238B; and

25 (4) the compound in which R¹ and R² are each hydroxy, R³ is allyl, R⁴ is methyl, n = 1, and the symbol of a line and a dotted line is a single bond. This compound is known as FR-900525.

With respect to the macrolide compounds (I) of this

invention, it is to be understood that there may be one or more conformers or stereoisomeric pairs such as optical and geometrical isomers due to asymmetric carbon atoms and double bonds, and such isomers are also
5 included within the scope of the present invention.

Salts of the macrolide compounds of the present invention include all pharmaceutically acceptable salts without limitation.

The macrolide compounds of the present invention may
10 be administered as pure compounds or mixtures of compounds or preferably, in a pharmaceutical vehicle or carrier.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation,
15 for example, in solid, semisolid or liquid form, which contains the macrolide compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, intravenous, intramuscular, or
20 parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions (saline, for example), emulsions, suspensions (in olive oil, for
25 example), and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable
30 for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes

may be used. The active object compound is included in the pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the disease.

5 Mammals which may be treated using the method of the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc., and humans.

10 For applying this composition to a human, it is preferable to apply it by oral, parenteral, enteral, intravenous, or intramuscular administration. While the dosage of therapeutically effective amount of the macrolide compounds varies from and also depends upon the age and condition of each individual patient to be
15 treated, in the case of a human, a daily dose of about 0.01-1000 mg, preferably 0.1-500 mg and more preferably 0.5-100 mg, of the active ingredient is generally given, and an average single dose of about 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally
20 administered.

Thus, the compounds of the present invention may be used for the treatment and prevention of diseases such as LTB₄-mediated diseases, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic
25 bowel disease, inflammatory bowel disease, necrotizing enterocolitis, and intestinal lesions resulting from thermal burns. In the present invention, the expression of the "ischemic diseases" includes the ischemia which occurs on transplantation.

30 For example, pretreatment of cats with FK 506 results in a dramatic reduction of mucosal myeloperoxidase (MPO) activity after ischemia and

reperfusion as compared to cats to which no drug was administered or to which cyclosporin A was administered. Further, pretreatment with FK 506 resulted in a significant reduction in the production or release of the potent neutrophil chemoattractant, LTB₄, as compared to either untreated cats or those treated with cyclosporin A.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Example 1.

METHODS

Fifteen cats were divided into 3 groups. Group 1, referred to as the untreated group, received no immunosuppressive agent. Group 2 received 25 mg/kg/day of cyclosporin A (CSA) in olive oil while group 3 received 0.3 mg/kg/day of FK 506 (Fujisawa Pharmaceutical Co., Osaka Japan) in interlipid. In the latter groups, the immunosuppressive agents were administered intramuscularly for three days prior to and on the day of the experiment.

Surgical Procedure. Experiments were performed using cats anesthetized with ketamine HCl and sodium pentobarbital. The experimental procedure has previously been described elsewhere (Granger et al, Gastroenterology, Vol. 81, p. 22 (1981)). Briefly, the small intestine was isolated from the ligament of Treitz to the ileocecal valve; the remainder of the small and

large intestine was extirpated. An arterial circuit was established between the superior mesenteric artery (SMA) and the left femoral artery. A square-wave, electromagnetic flowmeter (Carolina Medical Electronics, Inc.) was used to measure SMA blood flow. Systemic and SMA pressure were also monitored.

Experimental Protocol. Two mucosal biopsies were obtained under control conditions then SMA blood flow was reduced to 20% of control for a period of 3 hours. During the final 5 min. of ischemia, a second pair of mucosal biopsies was taken. The intestine was reperfused, and 1 hour later a third set of biopsies was obtained. From the first biopsy, mucosal myeloperoxidase (MPO) activity, a biochemical marker of neutrophil number, was determined using the method of Grisham et al., Am. J. Physiol., Vol. 251, p. G567 (1986). Mucosal production of LTB_4 was measured (see Mangino et al, Am. J. Physiol., Vol. 257, p. G299 (1989); Wallace et al, Euro. J. Pharmacol., Vol. 151, p. 43 (1988); and Salmon et al, Methods Enzymology, vol. 86, p. 477 (1982)) in tissue samples which were minced and then incubated for 30 min. at 37°C in 2.5 ml of 1 mM $CaCl_2$ and 1 mM $MgCl_2$ in phosphate buffered saline (pH 7.4). LTB_4 levels were then measured by a specific radioimmunoassay (Amersham, Arlington Heights, Illinois) using standard techniques.

Statistical Analyses. All data are expressed as means \pm S.E. Comparisons between the untreated and experimental groups were made using the Student's t-test for unpaired data.

30 RESULTS

The mucosal MPO value obtained for control (pre-

ischemic) conditions was 2.6 ± 0.6 Units/g wet weight of tissue. In untreated animals, mucosal MPO increased to 11.4 ± 2.4 Units/g and 23.9 ± 2.9 Units/g at 3 hours of ischemia and 1 hour of reperfusion, respectively. This reperfusion-induced increase in mucosal MPO is equivalent to an influx of 18 to 21 million neutrophils per gram of mucosa (Yokota et al, Transplant. Proc., vol. 21, p. 1066 (1989)). In animals pretreated with CsA and FK 506, the number of neutrophils emigrating into the mucosa after reperfusion was significantly reduced by 48% and 71%, respectively (see Figure 1). In addition, both agents decreased the influx of neutrophils induced by ischemia per se.

Mucosal LTB_4 synthesis did not differ among the three groups of animals during the control (pre-ischemic) period and at 3 hr. of ischemia (see Figure 2). During reperfusion, about a two-fold increase in LTB_4 synthesis was observed in the untreated group ($p < 0.05$). Although cyclosporin A did not alter the response of LTB_4 synthesis to reperfusion, FK 506 pretreatment resulted in a significantly lower increment in LTB_4 production during reperfusion.

Example 2.

	FK 506	1g
25	Hydroxypropyl methylcellulose 2910 (TC-5R)	1g
	Lactose	2g
	Croscarmellose sodium (Ac-Di-Sol)	1g

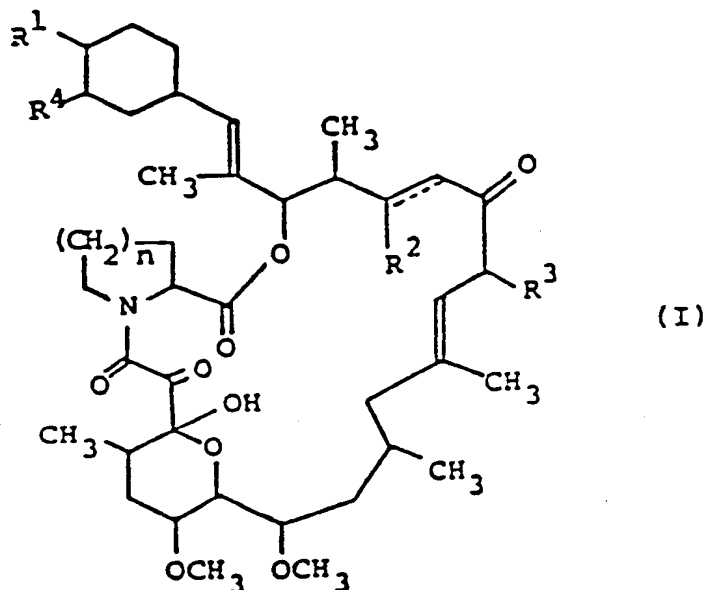
The FK 506 (1g) was dissolved in ethanol (10ml), and thereto was added hydroxypropyl methylcellulose 2910 (TC-5R) (1g) to prepare a suspension. To this suspension was added dichloromethane (5ml) to prepare a homogeneous solution. Lactose (2g) and croscarmellose sodium (Trade

Mark: Ac-Di-Sol, maker: Asahi Chemical Industry) were homogeneously suspended in this solution, and then the organic solvent was removed by evaporation. The residual product was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2 minutes by coffee mill and then passed through a sieve (32 mesh) to give the solid dispersion composition of FK 506 (5g). This composition was capsulated by a conventional manner to provide capsules containing 1mg or 5mg of FK 506 per each capsule.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described therein.

Claims

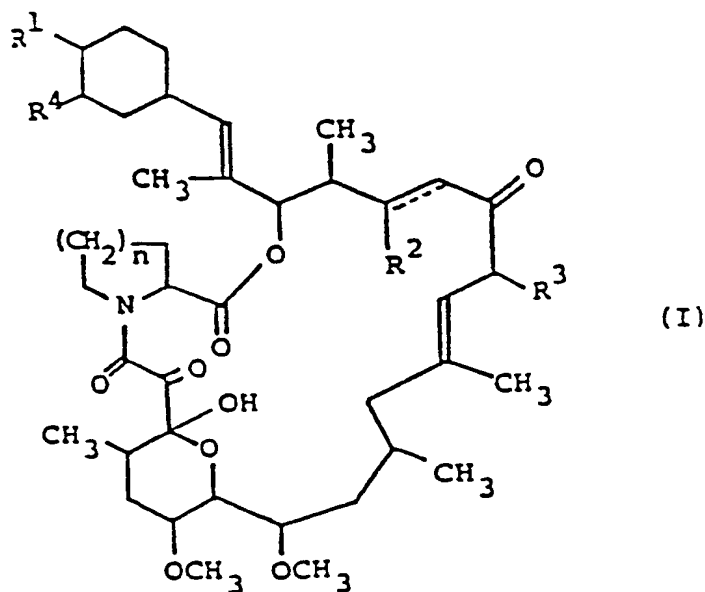
1. A method of preventing or treating inflammation of mucosa or blood vessels, comprising administering to a mammal in need thereof a pharmaceutically effective amount of a macrolide of formula I:



- wherein R^1 is hydroxy or protected hydroxy, R^2 is hydrogen, hydroxy or protected hydroxy, R^3 is methyl, ethyl, propyl or allyl, R^4 is hydroxy, methoxy or oxo, n is an integer of 1 or 2 and the symbol of a line and a dotted line is a single bond or a double bond, provided that R^2 is not protected hydroxy when R^4 is hydroxy or oxo, and salts thereof.

2. The method of Claim 1, wherein R^1 and R^2 are each hydroxy.
3. The method of Claim 2, wherein R^3 is allyl.
4. The method of Claim 1, wherein R^3 is ethyl.
5. The method of Claim 1, wherein R^3 is methyl.

6. The method of Claim 1, wherein R^4 is hydroxy.
7. The method of Claim 1, wherein R^4 is methoxy.
8. The method of Claim 1, wherein R^4 is oxo.
9. The method of Claim 1, wherein the macrolide is
5 FK 506.
10. The method of Claim 1, wherein said
administering is oral administration.
11. A method of preventing or treating LTB_4 -
mediated diseases, gastric ulcers, vascular damage caused
10 by ischemic diseases and thrombosis, ischemic bowel
disease, inflammatory bowel disease, necrotizing
enterocolitis, or intestinal lesions associated with
thermal burns comprising administering to a mammal in
need thereof a pharmaceutically effective amount of a
15 macrolide of the formula shown below:



wherein R^1 is hydroxy or protected hydroxy, R^2 is

hydrogen, hydroxy or protected hydroxy, R^3 is methyl, ethyl, propyl or allyl, R^4 is hydroxy, methoxy or oxo, n is an integer of 1 or 2 and the symbol of a line and a dotted line is a single bond or a double bond, provided
5 that R^2 is not protected hydroxy when R^4 is hydroxy or oxo, and salts thereof.

12. The method of Claim 11, wherein R^1 and R^2 are each hydroxy.

13. The method of Claim 12, wherein R^3 is allyl.

10 14. The method of Claim 11, wherein R^3 is ethyl.

15. The method of Claim 11, wherein R^3 is methyl.

16. The method of Claim 11, wherein R^4 is hydroxy.

17. The method of Claim 11, wherein R^4 is methoxy.

18. The method of Claim 11, wherein R^4 is oxo.

15 19. The method of Claim 11, wherein the macrolide is FK 506.

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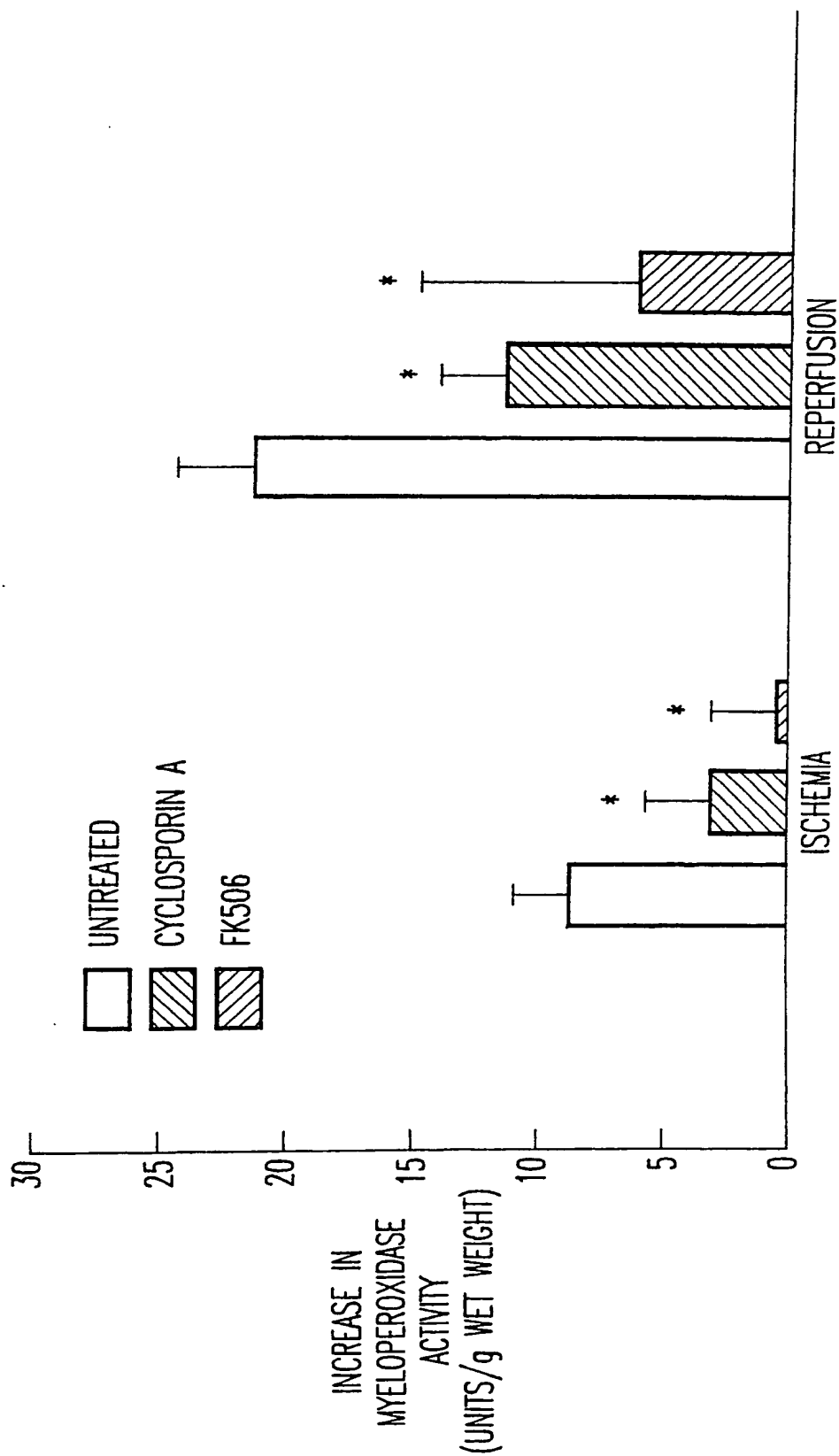


FIG. 1

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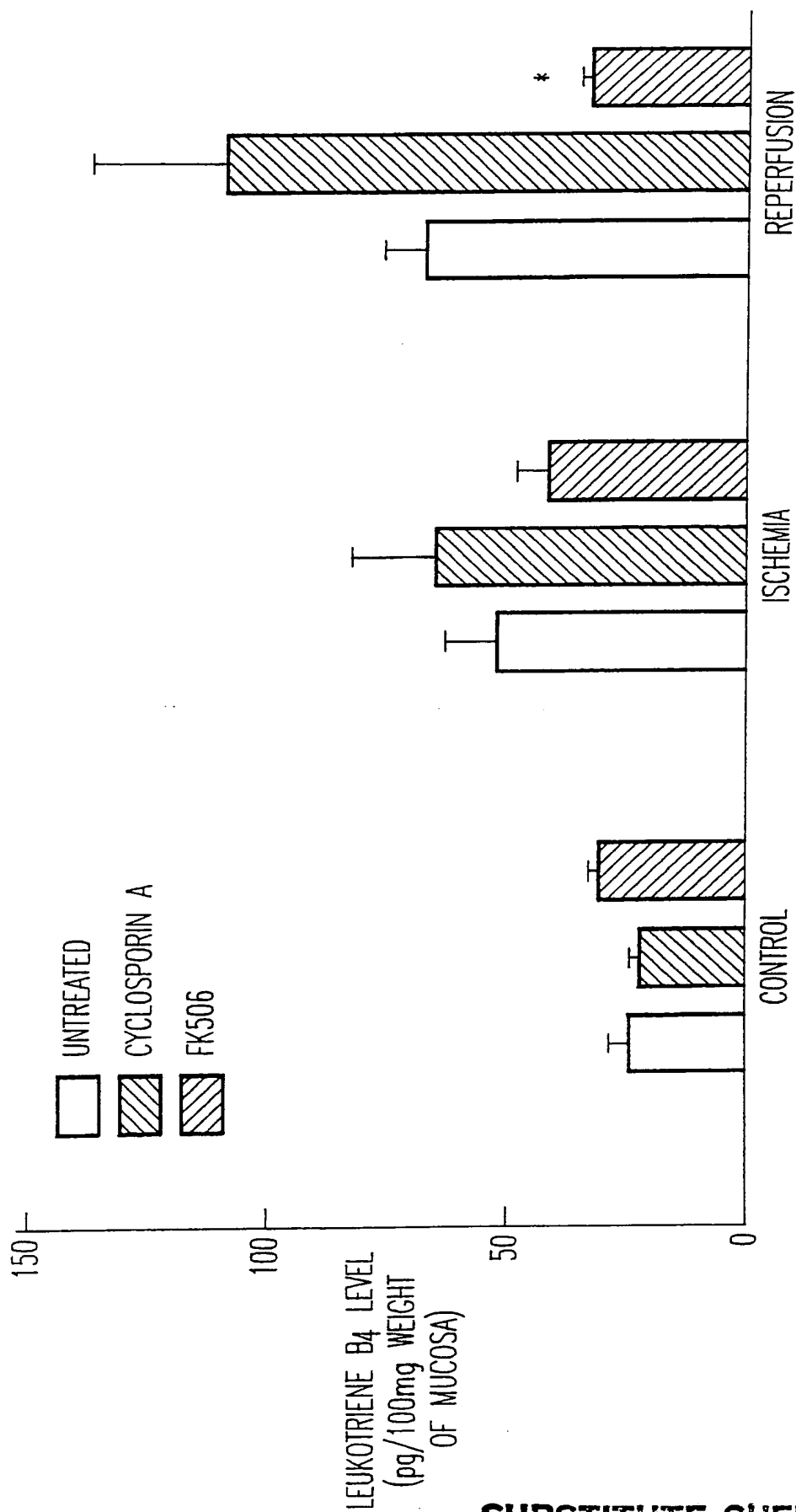


FIG. 2

SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/03185

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5): A61K 31/695; A61K 31/44; A61K 31/40 US CL : 514/63; 514/291; 514/411		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
US	514/63; 514/291; 514/411	
Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	US, A, 4,894,366 (OKUHARA) published 16 JANUARY 1990 See entire document	1-19
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 08 AUGUST 1991		Date of Mailing of this International Search Report <div style="font-size: 1.5em; font-weight: bold;">19 AUG 1991</div>
International Searching Authority ISA/US		Signature of Authorized Officer <div style="text-align: center;"> JEROME D. GOLDBERG </div> <div style="text-align: center; font-weight: bold;"> NGUYEN HUU HO INTERNATIONAL DIVISION </div>